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(54) Title: VALSARTAN TABLETS AND THE PROCESS FOR THE PREPARATION THEREOF

(57) Abstract: The present invention relates to valsartan tablets for oral administration comprising valsartan, at least two different disintegrants, and optionally hydrochlorthiazide (HCTZ); and processes of preparation thereof. The present invention also relates to methods of treating hypertension administering to a mammal a valsartan tablet disclosed herein.

VALSARTAN TABLETS AND THE PROCESS FOR THE PREPERATION THEREOF

Field of the Invention

The present invention relates to valsartan tablets for oral administration comprising valsartan, at least two different disintegrants, and optionally hydrochlorthiazide (HCTZ); and processes of preparation thereof. The present invention also relates to methods of treating hypertension administering to a mammal a valsartan tablet disclosed herein.

Background of the Invention

Valsartan is a non-peptide, orally active and specific angiotensin II antagonist acting on the AT_1 receptor subtype. Valsartan is chemically described as N-(1-oxopentyl)-N-{[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl}-L -valine. Presently valsartan tablets are marketed by Novartis as DIOVAN® in doses of 40, 80, 160 and 320 mg and it is indicated for the treatment of hypertension.

HCTZ is a loop diuretic and is chemically described as 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide. The combination of valsartan and HCTZ is indicated for treatment of hypertension in patients failing to achieve the desired effect with monotherapy. Fixed-dose combination tablets are marketed by Novartis as DIOVAN HCT® in doses of 80 mg/12.5 mg; 160 mg/12.5 mg and 160 mg/25 mg of valsartan/HCTZ respectively.

Both valsartan and HCTZ are fluffy materials having low density. Thus, preparation of solid dosage forms of acceptable size and suitable for oral administration is a challenging task.

U.S. Patent Nos. 6,294,197 and 6,485,745, assigned to Novartis, disclose the preparation of compressed tablets of valsartan by a dry granulation technique. The process comprises the steps of: blending valsartan, with or without HCTZ, and at least one pharmaceutically acceptable additive to form a mixture; subjecting the mixture to compression to form a coprimate; converting the coprimate into a granulate; and compressing the granulate to form the compressed tablet.

The process of compressing valsartan-containing tablets leads to the formation of a high-density product. However, high-density products are problematic in that they do not disintegrate satisfactorily, which leads to improper dissolution and sub-therapeutic concentration levels. Accordingly, there remains a need for a process to form valsartan tablets that exhibits good disintegration behavior.

Summary of the Invention

Generally provided herein are valsartan tablets, which disintegrate rapidly thereby enhancing dissolution properties, as well as processes of preparing such tablets and methods of treating hypertension by administering such tablets to a patient.

Thus provided herein are tablets comprising valsartan, and at least two disintegrants, wherein the at least two disintegrants are present intragranularly, extragranularly or both.

Embodiments of the tablets may include one or more of the following features. For example, the at least two disintegrants can comprise at least one intragranular disintegrant and at least one extragranular disintegrant. The intragranular disintegrant and the extragranular disintegrant can be the same or different. The at least one intragranular disintegrant and the at least one extragranular disintegrant can also be present in a ratio from about 1:1 to about 1:0.1.

The at least two disintegrants can be independently selected from starch, starch glycolate, crospovidone; cellulose-based disintegrants, or mixtures thereof. Preferably, the at least two disintegrants can be crospovidone and at least one additional disintegrant, for example, can be one or more cellulose-based disintegrants, which can include hydroxypropylcellulose-low substituted (L-HPC), carboxy methylcellulose calcium, carboxy methylcellulose sodium, croscarmellose sodium or mixtures thereof.

The concentration of the at least two disintegrants can be from about 1% w/w to 80% w/w. When crospovidone is present, the concentration of crospovidone can be from about 1% w/w to about 60% w/w. The one or more cellulose-based disintegrants can be L-HPC, wherein L-HPC can be present at a concentration from about 1% w/w to about 60% w/w.

The tablet can further comprise 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide (HCTZ). The tablet can further comprise one or more pharmaceutically acceptable additives, for example, binders, diluents, lubricants/glidants, coloring agents or mixtures thereof.

The tablet can be further coated with one or more non-functional coating layers comprising one or more film-forming polymers, for example, ethylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, methylcellulose, carboxymethylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropyl methyl phthalate, cellulose acetate, cellulose acetate trimelliatate, cellulose acetate phthalate; waxes, methacrylic acid polymers, or mixtures thereof.

Also provided herein are processes for the preparation of valsartan tablets comprising the steps of blending valsartan and at least two disintegrants to form a blend, and compressing the blend into a tablet.

Embodiments of the processes can include one of more of the following features. For example, step (a) can comprise:

blending HCTZ, valsartan, at least two disintegrants, optionally one or more lubricants/glidants, optionally one or more diluents, and optionally one or more binders to form a blend,

blending one or more binders, valsartan, at least two disintegrants, optionally one or more lubricants/glidants, optionally one or more diluents and optionally HCTZ to form a blend,

blending one or more lubricants/glidants, valsartan, at least two disintegrants, optionally one or more binders, optionally one or more diluents and optionally HCTZ to form a blend, or

blending one or more diluents, valsartan, at least two disintegrants, optionally one or more binders, optionally one or more lubricants/glidants and optionally HCTZ to form a blend.

The process can further comprise the step of (c) coating the tablet with one or more non-functional layers.

Also provided herein are processes for the preparation of valsartan tablet comprising the steps of blending valsartan and at least one intragranular disintegrant to form a first blend, granulating the first blend into a granulate, blending the granulate with at least one extragranular disintegrant to form a second blend, and compressing the second blend into a tablet, wherein the at least one intragranular disintegrant and the at least one extragranular disintegrant are the same or different.

Embodiments of the processes can include one or more of the following features. For example, step (a) can comprise blending valsartan, at least one intragranular disintegrant, one or more diluents, and one or more binders to form a first blend; or blending valsartan, at least one intragranular disintegrant, and HCTZ to form a first blend.

Step (c) can comprise blending the granules with at least one intragranular disintegrant and one or more lubricants/glidants to form a second blend.

The at least one intragranular disintegrant can be L-HPC and crospovidone and the at least one extragranular disintegrant is crospovidone. The granules can be prepared by a wet granulation or dry granulation.

The tablet can also be coated with one or more non-functional coating layers. The one or more non-functional coating layers can be coated on the tablet as a solution/dispersion of one or more coating components in one or more solvents selected from methylene chloride, isopropyl alcohol, acetone, methanol, ethanol, water or mixtures thereof.

Also provided herein are methods of treating hypertension comprising administering to a mammal in need thereof a valsartan tablet comprising valsartan, and at least two disintegrants, wherein the disintegrants are present intragranularly, extragranularly or both. Embodiments of the methods can include one or more of the following features. For example, one of the at least two disintegrants can be crospovidone. The tablet can further comprise HCTZ.

Detailed Description of the Invention

The present invention relates to processes of manufacturing valsartan tablets, which disintegrate rapidly thereby enhancing dissolution properties. Such good disintegrating behavior and dissolution properties can be facilitated, for example, by using

particular combinations of disintegrants, *e.g.*, by using at least two disintegrants. Such disintegrants may be present intragranularly or extragranularly or both.

The present invention also relates to valsartan tablets having at least one intragranular and one extragranular disintegrant, wherein the combination of intragranular and extragranular disintegrants are different. Such valsartan tablets provide more desirable disintegration and dissolution properties.

Thus in one general aspect, there is provided valsartan tablets comprising valsartan and at least two disintegrants.

In another general aspect, there is provided valsartan tablets comprising valsartan, at least one intragranular and one extragranular disintegrant, wherein the intragranular and extragranular disintegrants may be different.

In another general aspect, there is provided valsartan tablets comprising valsartan, crospovidone and at least one additional disintegrant other than crospovidone.

In another general aspect, there is provided valsartan tablets comprising valsartan, crospovidone and at least one cellulose-based disintegrant.

In another general aspect, there is provided processes for the preparation of valsartan tablets comprising the steps of: a) blending valsartan and at least two disintegrants to form a blend and b) compressing the blend into a tablet.

In another general aspect, there is provided processes for the preparation of valsartan tablets comprising the steps of: a) blending valsartan and at least one intragranular disintegrant to form a blend b) granulating the blend into a granulate, c) blending the granulate with at least one extragranular disintegrant to form a second blend and d) compressing the second blend into a tablet; wherein the intragranular and extragranular disintegrants may be the same or different.

In another general aspect, there is provided methods for the treatment of hypertension in a mammal in need thereof by administering to the mammal a valsartan tablet comprising a therapeutically effective amount of valsartan and at least two disintegrants.

In another general aspect, there is provided methods for the treatment of hypertension in a mammal in need thereof by administering to the mammal a valsartan tablet comprising a therapeutically effective amount of valsartan, at least one intragranular disintegrant and at least one extragranular disintegrant, wherein the at least one intragranular disintegrant and extragranular disintegrants may be different.

In another general aspect, there is provided a method for the treatment of hypertension in a mammal in need thereof by administering to the mammal a valsartan tablet comprising a therapeutically effective amount of valsartan, crospovidone and at least one additional disintegrant other than crospovidone.

Valsartan tablets of any of the aspects above may further comprise HCTZ (6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide). Tablets comprising HCTZ may be prepared by incorporating HCTZ in a blend comprising valsartan.

The term "valsartan," as used herein, may include free acid forms of valsartan and pharmaceutically acceptable salts thereof. Valsartan may be used in an amount which either reduces or halts the progress of the pathological condition being treated or which otherwise cures the condition partly or completely; and the amount may vary from about 10 to about 350 mg. In addition to valsartan, the tablet may also comprise from about 6 to about 60 mg HCTZ or pharmaceutically acceptable salt thereof.

The term "disintegrants," as used herein, includes all physiologically inert disintegrants used in the pharmaceutical art of dispensing. Examples include starch, starch glycolate, crospovidone, and cellulose-derivatives (*e.g.*, hydroxypropylcellulose-low substituted (L-HPC), carboxy methylcellulose calcium, carboxy methylcellulose sodium, croscarmellose sodium, and the like), or mixtures thereof. The concentration of disintegrants may vary from about 1% w/w to about 80% w/w. In one example, crospovidone and L-HPC may be used from about 1% w/w to about 60% w/w and about 1% w/w to about 60% w/w, respectively. In certain embodiments where tablets comprise both intragranular and extragranular disintegrants, their ratio may vary from about 1:1 to about 1:0.1.

The use of suitable combinations of disintegrants, as well as their amounts and ratios, improve the *in vitro* and *in vivo* performance of the tablets, by enhancing its disintegration, and consequently the dissolution rate.

In addition to disintegrants, valsartan tablets of the present invention may further comprise one or more pharmaceutically acceptable additives, which can, for example, provide bulk and aid in processing.

The phrase "pharmaceutically acceptable additive," as used herein, includes all physiologically inert additives used in the pharmaceutical art of dispensing. Examples include binders, diluents, lubricants/glidants, coloring agents, and the like, or mixtures thereof.

Examples of binders include methyl cellulose, hydroxypropylcellulose, polyvinylpyrrolidone, gelatin, gum Arabic, ethylcellulose, polyvinyl alcohol, pullulan, pregelatinized starch, agar, tragacanth, sodium alginate, propylene glycol, and the like, or mixtures thereof.

Examples of diluents include calcium carbonate, calcium phosphate-dibasic, calcium phosphate-tribasic, calcium sulfate, microcrystalline cellulose, silicified microcrystalline cellulose, cellulose powdered, dextrates, dextrins, dextrose excipients, fructose, kaolin, lactitol, lactose, mannitol, sorbitol, starch, starch pregelatinized, sucrose, sugar compressible, sugar confectioners, and the like, or mixtures thereof.

Examples of lubricants and glidants include silicon dioxide, colloidal silicon dioxide, stearic acid, magnesium stearate, calcium stearate, talc, hydrogenated castor oil, sucrose esters of fatty acids, microcrystalline wax, yellow beeswax, white beeswax and the like, or mixtures thereof.

The coloring agents may be selected from any FDA approved color agents for oral use.

The valsartan tablets may further be coated with one or more non-functional layers comprising film-forming polymers with or without other coating additives, if desired. Examples of film forming polymers include ethylcellulose, hydroxypropyl ethylcellulose, hydroxypropylcellulose, methylcellulose, carboxymethylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropyl methyl phthalate,

cellulose acetate, cellulose acetate trimelliatate, cellulose acetate phthalate; waxes such as polyethylene glycol; methacrylic acid polymers, *e.g.*, EUDRAGIT® RL and RS; and the like or mixtures thereof. Alternatively, commercially available coating compositions comprising film-forming polymers marketed under various trade names, *e.g.*, OPADRY®, may also be used as a coating.

Valsartan tablets disclosed herein can be prepared by processes comprising the steps of: (a) blending valsartan and at least two disintegrants to form a blend and (b) compressing the blend into a tablet.

In one embodiment, valsartan tablets disclosed herein can be prepared by processes comprising the steps of: (a) blending valsartan with one or more diluents, one or more binders, at least two disintegrants, and one or more lubricants/glidants to form a blend, (b) compressing the blend to form a tablet, and (c) optionally coating the tablet with one or more non-functional layers.

In another embodiment, valsartan and HCTZ tablets disclosed herein can be prepared by processes comprising the steps of: (a) blending valsartan and HCTZ with one or more diluents, one or more binders, at least two disintegrants, and one or more lubricants/glidants to form a blend, (b) compressing the blend to form a tablet, and (c) optionally coating the tablet with one or more non-functional layers.

In one embodiment, valsartan tablet disclosed herein can be prepared by processes comprising the steps of: (a) blending valsartan with one or more diluents, one or more binders, and at least one intragranular disintegrants to form a blend, (b) granulating the blend to form granules, (c) blending the granules with at least one extragranular disintegrant, and one or more lubricants/glidants to form a second blend, (d) compressing the second blend to form a tablet, and (e) optionally coating the tablet with one or more non-functional layers.

In another embodiment, valsartan and HCTZ tablets disclosed herein can be prepared by processes comprising the steps of: (a) blending valsartan and HCTZ with one or more diluents, one or more binders, and at least one intragranular disintegrants to form a blend, (b) granulating the blend to form granules, (c) blending the granules with at least one extragranular disintegrant, and one or more lubricants/glidants to form a second blend,

(d) compressing the second blend to form a tablet, and (e) optionally coating the tablets with one or more non-functional layers.

In another embodiment, valsartan tablets disclosed herein can be prepared by processes comprising the steps of: (a) blending valsartan with one or more diluents, one or more binders, L-HPC and crospovidone as intragranular disintegrants to form a blend, (b) dry granulating the blend to form granules, (c) blending the granules with crospovidone as extragranular disintegrant, and one or more lubricants/glidants to form a second blend, (d) compressing the second blend to form a tablet, and (e) coating the tablet with one or more non-functional layers.

In another embodiment, valsartan and HCTZ tablets disclosed herein can be prepared by processes comprising the steps of: (a) blending valsartan and HCTZ with one or more diluents, one or more binders, L-HPC and crospovidone as intragranular disintegrants to form a blend, (b) dry granulating the blend to form granules, (c) blending the granules with crospovidone as extragranular disintegrant, and one or more lubricants/glidants to form a second blend, (d) compressing the second blend to form a tablet, and (e) coating the tablet with one or more non-functional layers.

Granules may be prepared either by wet granulation or dry granulation techniques known to the skilled artisan. Dry granulation may be carried out, for example, by using a roller compactor and compacted at a compaction pressure of about 25-75 bar, more preferably from about 35-65 bar, at a roller speed from about 1-10 rpm, more preferably from 2-5 rpm. The screw-feeder rate can be maintained at about 10-60 rpm, more preferably at about 20-50 rpm and the distance between the roller can be adjusted between about 0.1 to 1.0 mm, more preferably between about 0.2 to 0.5 mm.

Alternatively, dry granulation may also be carried out, for example, by the process of slugging.

Wet granulation may be carried out, for example, by incorporating binder in the blend comprising valsartan and granulating with aqueous and/or non aqueous granulating fluids. Alternatively, binder may be dissolved/dispersed in granulating fluid.

The optional one or more non-functional coating layers may be applied, for example, as one or more solutions or dispersions of one or more film-forming polymers

with or without other coating additives. Such optional one or more non-functional coating layers can be applied using any conventional techniques known in the art, *e.g.*, spray coating in a conventional coating pan or fluidized bed processor; dip coating and the like.

Examples of solvents used as granulating fluids and for preparing a solution/dispersion of the coating components include methylene chloride, isopropyl alcohol, acetone, methanol, ethanol, water or mixtures thereof.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are included within the scope of the present invention. The examples are provided to illustrate particular aspects of the disclosure and do not limit the scope of the present invention as defined by the claims.

Examples

Table 1. Valsartan tablet compositions

Ingredient	1	2	3	4	5
	Amount (mg/core)				
Intragranular					
Valsartan	320.0	320.0	320.0	320.0	320.0
Crospovidone	302.5	302.5	302.5	-	302.5
L-HPC*	80.0	80.0	-	598.5	-
Ca-CMC**	85.0	-	85.0	-	110.0
Croscarmellose sodium	-	85.0	80.0	-	110.0
Microcrystalline cellulose	50.0	50.0	50.0	-	73.0
Starch	81.0	81.0	81.0	-	3.0
Colloidal silicon dioxide	55.0	55.0	55.0	55.0	55.0
Magnesium stearate	16.5	16.5	16.5	16.5	16.5
Extragranular					
Microcrystalline cellulose	55.0	55.0	55.0	55.0	55.0
Crospovidone	27.5	27.5	27.5	27.5	27.5
Colloidal silicon dioxide	5.5	5.5	5.5	5.5	5.5
Talc	11.0	11.0	11.0	11.0	11.0
Magnesium stearate	11.0	11.0	11.0	11.0	11.0

* Low substituted hydroxypropyl cellulose; ** Carboxymethyl cellulose

Procedure:

1. Valsartan was sifted through #44 BSS and blended with all other intragranular ingredients except magnesium stearate in a low shear blender for about 20-30 minutes.
2. The blend of step 1 was sifted and mixed with magnesium stearate for 5 minutes.
3. The blend of step 2 was compacted at a compaction pressure of about 25-75 bar in a roller compactor.
4. The compacts obtained from step 3 were milled in an oscillating granulator fitted with a screen of 0.5 mm.
5. The sized granules from step 4 were blended with extragranular ingredients and compressed into suitable-sized tablets.
6. The tablets were then coated with aqueous Opadry® to a weight build-up of about 3.0 to 4.0% w/w.

The tablets of Examples 1, 2 and 3 were tested for *in vitro* release of valsartan in USP type II dissolution apparatus at a temperature of 37±0.5 °C, in 900 mL of 0.067M phosphate buffer (pH 6.8). The samples were analyzed for valsartan content using UV spectroscopic method. The *in vitro* release profile of valsartan tablets are shown in Table 2.

TABLE 2: *In vitro* release profile of valsartan tablets

Time (minutes)	Cumulative percentage (%) of valsartan released		
	Ex 1	Ex 2	Ex 3
5	94.0	92.0	95.0
10	94.0	93.0	97.0
20	95.0	95.0	99.0
30	95.0	95.0	99.0

While several particular forms of the invention have been described, it will be apparent that various modifications and combinations of the inventions detailed in the text can be made without departing from the spirit and scope of the inventions. Although all

the examples relate to tablets comprising 320 mg of valsartan, it will be apparent to one skilled in the art that tablets comprising lower amount of valsartan *i.e.*, 40, 80 or 160 mg may also be prepared using the above relative compositions and processes.

Although dry granulation technique is used for preparing valsartan tablets, as given in the examples, wet granulation and direct compression can also be used for preparing valsartan tablets.

WE CLAIM:

1. A tablet comprising:

valsartan, and

at least two disintegrants,

wherein the at least two disintegrants are present intragranularly, extragranularly or both.

2. The tablet of claim 1, wherein the at least two disintegrants comprise at least one intragranular disintegrant and at least one extragranular disintegrant.

3. The tablet of claim 2, wherein the intragranular disintegrant and the extragranular disintegrant are the same or different.

4. The tablet of claim 2, wherein the at least one intragranular disintegrant and the at least one extragranular disintegrant is present in a ratio from about 1:1 to about 1:0.1.

5. The tablet according to claim 1, wherein the at least two disintegrants are independently selected from starch, starch glycolate, crospovidone; cellulose-based disintegrants, or mixtures thereof.

6. The tablet of claim 5 comprising crospovidone and at least one additional disintegrant.

7. The tablet of claim 6, wherein the at least one additional disintegrant is one or more cellulose-based disintegrants.

8. The tablet of claim 7, wherein the one or more cellulose-based disintegrants are selected from hydroxypropylcellulose-low substituted (L-HPC), carboxy methylcellulose calcium, carboxy methylcellulose sodium, croscarmellose sodium or mixtures thereof.

9. The tablet of claim 1, wherein the concentration of the at least two disintegrants is from about 1% w/w to 80% w/w.

10. The tablet of claim 6, wherein the concentration of crospovidone is from about 1% w/w to about 60% w/w.

11. The tablet of claim 8, wherein the one or more cellulose-based disintegrants is L-HPC, wherein L-HPC is present at a concentration from about 1% w/w to about 60% w/w.

12. The tablet of claim 1 further comprising 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide (HCTZ).

13. The tablet of claim 1 further comprising one or more pharmaceutically acceptable additives.

14. The tablet of claim 13, wherein the one or more pharmaceutically acceptable additives is selected from binders, diluents, lubricants/glidants, coloring agents or mixtures thereof.

15. The tablet of claim 1, wherein tablet is further coated with one or more non-functional coating layers comprising one or more film-forming polymers.

16. The tablet of claim 15, wherein the film-forming polymers is ethylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, methylcellulose, carboxymethylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropyl methyl phthalate, cellulose acetate, cellulose acetate trimelliatate, cellulose acetate phthalate; waxes, methacrylic acid polymers, or mixtures thereof.

17. A process for the preparation of valsartan tablets comprising the steps of:

(a) blending valsartan and at least two disintegrants to form a blend, and

(b) compressing the blend into a tablet.

18. The process of claim 17, wherein step (a) comprises:

blending HCTZ, valsartan, at least two disintegrants, optionally one or more lubricants/glidants, optionally one or more diluents, and optionally one or more binders to form a blend,

blending one or more binders, valsartan, at least two disintegrants, optionally one or more lubricants/glidants, optionally one or more diluents and optionally HCTZ to form a blend,

blending one or more lubricants/glidants, valsartan, at least two disintegrants, optionally one or more binders, optionally one or more diluents and optionally HCTZ to form a blend, or

blending one or more diluents, valsartan, at least two disintegrants, optionally one or more binders, optionally one or more lubricants/glidants and optionally HCTZ to form a blend.

19. The process of claim 17, wherein the process further comprises the step of:

(c) coating the tablet with one or more non-functional layers.

20. A process for the preparation of valsartan tablet comprising the steps of:

(a) blending valsartan and at least one intragranular disintegrant to form a first blend,

(b) granulating the first blend into a granulate,

(c) blending the granulate with at least one extragranular disintegrant to form a second blend, and

(d) compressing the second blend into a tablet,

wherein the at least one intragranular disintegrant and the at least one extragranular disintegrant are the same or different.

21. The process of claim 20, wherein step (a) comprises: blending valsartan, at least one intragranular disintegrant, one or more diluents, and one or more binders to form a first blend; or blending valsartan, at least one intragranular disintegrant, and HCTZ to form a first blend.

22. The process claim 20, wherein step (c) comprises blending the granules with at least one intragranular disintegrant and one or more lubricants/glidants to form a second blend.

23. The process of claim 20, wherein the at least one intragranular disintegrant is L-HPC and crospovidone and the at least one extragranular disintegrant is crospovidone.

24. The process of claim 20, wherein the granules are prepared by a wet granulation or dry granulation.

25. The process of claim 20, wherein tablet is coated with one or more non-functional coating layers.

26. The process of claim 25, wherein the one or more non-functional coating layers are coated on the tablet as a solution/dispersion of one or more coating components in one or more solvents selected from methylene chloride, isopropyl alcohol, acetone, methanol, ethanol, water or mixtures thereof.

27. A method of treating hypertension comprising administering to a mammal in need thereof a valsartan tablet comprising valsartan, and at least two disintegrants, wherein the disintegrants are present intragranularly, extragranularly or both.

28. The method of claim 27, wherein one of the at least two disintegrants is crospovidone.

29. The method of claim 27, wherein the tablet further comprises HCTZ.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB2005/000578

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/20 A61K31/41 A61K31/549 A61P9/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97/49394 A (NOVARTIS AG; WAGNER, ROBERT, FRANK; KATAKUSE, YOSHIMITSU; TAIKE, TAKAS) 31 December 1997 (1997-12-31) the whole document in particular examples 3,3A	1-29
X	US 2002/155986 A1 (BULLOCK GILLIAN ROSEMARY ET AL) 24 October 2002 (2002-10-24) paragraph '0132! - paragraph '0166! paragraph '0192! - paragraph '0197!	1-29
A	EP 0 747 050 A (BRISTOL-MYERS SQUIBB COMPANY; SANOFI-SYNTHELABO) 11 December 1996 (1996-12-11) the whole document	

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 June 2005	05/07/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hornich, E

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB2005/000578

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 2004/100857 A (AKINA, INC) 25 November 2004 (2004-11-25) the whole document	1-29

Form PCT/ISA/210 (continuation of second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2005/000578

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 27-29 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

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Inter[redacted]al Application No
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